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on Drugs and Therapeutics

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CYCLAMYCIN AND TAO

Wyeth calls Cyclamycin (its brand name for triacetyloleandomycin) a "workhorse mycin for common infections." That description fits neither Cyclamycin nor TAO (Pfizer's brand of the same antibiotic), nor any other antibiotic now available. Triacetyloleandomycin is, however, an occasionally useful addition to the small list of antibiotics effective against resistant strains of staphylococci.

Triacetyloleandomycin has the same actions and uses as oleandomycin phosphate (derived from Streptomyces antibioticus), but according to the Council on Drugs (JAMA, 10/25/58), after oral administration it is absorbed from the intestinal tract more rapidly and completely than the phosphate and produces higher blood levels. Although the drug sometimes causes gastrointestinal irritation, no serious reactions such as anaphylaxis, micrococcal enteritis or blood dyscrasias have been reported thus far; however, the antibiotic has been in use for too short a period to be certain of the range and severity of its side effects.

WHAT IT'S GOOD FOR - Although triacetyloleandomycin and erythromycin are similar in in vitro effectiveness and in spectrum of bacterial action (most Gram-positive and some Gram-negative organisms), the results of a comparative study of the two antibiotics by a Mayo team (A. J. Reisch et al, Proceedings of Staff Meeting of Mayo Clinic, 4/16/58) indicate that erythromycin "appears preferable in infections due to [organisms] sensitive to both agents." However, about 25 per cent of staphylococci strains are now resistant to erythromycin, and of these about two-thirds show in vitro sensitivity to triacetyloleandomycin. If the organism proves resistant to erythromycin and shows in vitro sensitivity to triacetyloleandomycin, the latter antibiotic should then be employed. (There is no doubt that staphylococci can acquire resistance to this as to other antibiotics.)

If a strain is resistant to both erythromycin and triacetyloleandomycin, then novobiocin (Albamycin - Upjohn; Cathomycin - Merck) can be tried. However, strains resistant to novobiocin have already begun to appear, and this valuable drug should not be used where erythromycin or triacetyloleandomycin can be successfully employed (D. R. Nichols and W. J. Martin, Surgery, Gynecology & Obstetrics 107, 523-526, 1958). For severe staphylococcus infections resistant to all of the above agents and to penicillin, there are available chloramphenicol (Chloromycetin - Parke, Davis) and the parenteral antibiotics, kanamycin (Kantrex - Bristol), neomycin, ristocetin (Spontin - Abbott), and vancomycin (Vancocin - Lilly). Vancomycin appears to have the least severe toxic and side effects of these parenteral antibiotics in the treatment of severe staphylococcus infections resistant to oral therapy.

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Triacetyloleandomycin is recommended by the producers for the treatment of infections by H. influenzae, gonococci and meningococci. The AMA Council on Drugs considers the evidence to substantiate such use inadequate, however. While the Council finds the antibiotic useful against beta-hemolytic streptococci and pneumococci, it points out that penicillin and the tetracyclines are considered the agents of choice with these organisms. The antibiotic choice for severe H. influenzae infection is chloramphenicol; for gonococci, penicillin; and for meningococci infections, the sulfonamides. (NOTE: Lilly has just introduced a new erythromycin salt – erythromycin propionate [Ilosone]. Preliminary reports indicate that it gives effective tissue concentrations in lower doses than the older erythromycin preparations, thereby reducing the frequency of gastrointestinal symptoms. The Medical Letter will report on erythromycin propionate in a coming issue.)

MARSILID

Early in 1958, reports of jaundice, severe liver damage and death following the use of Marsilid (Hoffman-LaRoche's brand name for iproniazid), put a stop to the promotion of this drug as a "psychic energizer" for the relief of severe depression. Now the promotion is getting under way again, the justification being that the great therapeutic benefits attributed to Marsilid warrant the risk even of fatal toxic effects. (The drug is also claimed to be useful for rheumatoid arthritis and angina pectoris.)

We do not question the good faith in which the justification is offered. After careful review of the evidence, however, we do question whether Marsilid has any proper place in the therapy of depression or of other conditions except, perhaps, in controlled institutional settings where the patient can be supervised continuously, and where liver function tests can be made at least weekly.

SMALL DOSES HAZARDOUS - For a time it was thought that only large doses of Marsilid (150 mg. or more per day) caused severe liver damage and death, and 50-mg. doses were recommended. Recent investigations have shown that lower doses taken for relatively short periods can cause fatal liver damage. Furthermore, while Marsilid clearly causes central-nervous-system stimulation and has benefited some severely depressed patients, its action in any individual is highly unpredictable; its use must, therefore, be considered experimental, and experimentation is rarely justified when the potential for damage is so great.

How frequently mild liver injury follows administration of Marsilid is unknown, though in one study of tuberculosis patients a few years ago, nine of 52 patients who had been on Marsilid therapy showed evidence of impaired liver function. But cases of severe liver damage have been the subject of a number of studies; the latest and one of the most thorough of these was reported recently by M. Kahn and V. Perez (American Journal of Medicine, Dec. '58). Of nine cases of severe liver damage studied by the authors, six had received Marsilid for depression and three for angina pectoris. Two of the patients died with massive necrosis of the liver. According to the authors, "The dose of iproniazid does not appear to be related to the onset of jaundice and...lowering the dose [does not] lessen the danger....In view of the unpredictability of occurrence, rapidity of progression and lack of relation to dosage...the use of iproniazid should be reserved for those few patients in whom the potential benefits from the drug are of such degree as to outweigh the possible development of severe hepatic necrosis with possible fatal outcome."

OTHER WARNINGS - In another study of 13 biopsy and 16 autopsy specimens from 27 patients (JAMA, 12/27/58), Dr. Hans Popper concludes that whatever the causal relationship, "...the possible occurrence of severe hepatic damage with a deceptively less severe clinical picture but with a high mortality should be kept in mind when iproniazid is administered and should be weighed against its definite usefulness in patients with disabling depression." According to the Council on Drugs (JAMA, 9/20/58), "The relatively high incidence of postural hypotension after Marsilid therapy with the attending danger of fractures or lacerations from falls [makes] the use of the drug particularly hazardous in geriatric patients." This hazard alone is enough to rule out the use of Marsilid in the sector of the population in which mental depression is so frequent.

Weighing all the therapeutic benefits against all the risks, the conclusion is inescapable that cases warranting the use of the drug are indeed rare. Milder forms of depression can often be treated by the physician with psychotherapy and the safer central-nervous-system stimulants such as the amphetamines. It is to be hoped that less toxic analogues of iproniazid will be developed to fulfill the therapeutic promise of this drug without its dangerous side effects.

A NEW DRUG FOR DEPRESSION - A new central-nervous-system stimulant for the treatment of severe depression is now being clinically tested by a number of investigators. The drug, imipramine hydrochloride (Tofranil - Geigy), seems to offer considerable promise. No serious toxic reactions have yet been reported, though it is too early to be sure that none will appear. Release of the drug is not planned before July.

ASPIRIN, BUFFERIN AND ECOTRIN

A Bufferin tablet contains 5 grains of aspirin and 140 milligrams of antacid. It is promoted to the medical profession as well as to consumers with the claim that it induces less "stomach irritation" and acts more rapidly than "regular" aspirin. Frequent repetition and numerous references to favorable clinical tests have led to wide acceptance of the claims.

Many physicians doubtless missed the reports on three well-controlled clinical trials comparing ordinary aspirin tablets and Bufferin, two in the New England Journal of Medicine (1/30/58), and one in Postgraduate Medicine (8/58). Since the promotion of Bufferin to physicians continues, reference to these reports is still in order. As the lead editorial in the same issue of the New England Journal of Medicine sums it up, the objective data of the two studies reported in the Journal "...certainly make such claims as 'less stomach irritation' and 'acts twice as fast' highly questionable, to say the least....Unquestionably, the medicine shows technic has again demonstrated the power of its approach."

FOR GASTRIC IRRITATION - There is no doubt that in some patients, aspirin and other salicylates can cause varying degrees of stomach irritation, and occasionally even hemorrhage. But there is considerable doubt that Bufferin offers more security from these side effects than plain aspirin. In some patients, gastric irritation results from the action of the rapidly disintegrating aspirin on the stomach mucosa. Drinking a full tumbler of water with the aspirin may reduce such irritation. If an antacid is needed, a small pinch (about 1 gram) of bicarbonate of soda (or for long-term use, calcium carbonate) with each aspirin tablet will

control gastric irritation much more effectively than the 140 milligrams of antacid in a tablet of Bufferin.

Ecotrin (Smith, Kline & French) enteric-coated aspirin tablets have also been promoted for use where gastric irritation is a problem. The history of enteric coatings is replete with failures – unduly rapid disintegration, or often failure of the coating to disintegrate at all so that the tablets are excreted intact. Reports of clinical trials indicate that Ecotrin will probably escape disintegration in the stomach and thus prevent stomach irritation. However, the reports fail to provide convincing evidence of complete disintegration in the intestine or the development of effective salicylate blood levels. (Bufferin tablets cost $1.23 per 100; Ecotrin, $1.50 per 100; Aspirin Tablets U.S.P., about 25¢ to 70¢ per 100).

DIETARY AIDS FOR REDUCING BLOOD CHOLESTEROL

Physicians and consumers are offered many dietary aids for the reduction of elevated blood cholesterol. The ostensible purpose of the reduction is to help prevent or treat atherosclerosis and its complications – coronary artery disease and strokes. Despite numerous reports and claims, however, the evidence is far from conclusive that there is a cause-and-effect relationship between blood lipids and atherosclerosis and its complications; and there is no proof that a successful reduction of blood cholesterol is accompanied by a halt or regression in the atherosclerotic changes in the coronary, cerebral or other arteries (W. C. Felch, L. Sinisterra, T. B. Van Itallie, and F. J. Stare, Vitamins and Hormones, Vol. 16, 1958).

Any effort to manage elevated blood cholesterol associated with coronary artery and cerebrovascular disease by drugs or dietary aids must be considered purely experimental. If it is desired experimentally to attempt a reduction of blood cholesterol in patients with hypercholesterolemia, three ounces of corn oil (as in Mazola) may be taken daily along with a diet containing less than 25 grams of animal fat. (Note that corn oil causes loose stools in some patients.) In place of or in addition to corn oil, sitosterols (Cytellin - Lilly) may be tried in recommended doses, or the patient may take 3 to 6 grams of nicotinic acid daily (Council on Drugs, JAMA, 11/29/58). However, the full range of side effects of sitosterols and of nicotinic acid in the large dosage required for effectiveness is still to be determined. The daily dosage of corn oil costs about 6¢, of Cytellin, about 70¢, of nicotinic acid, about 20¢ to 40¢.

Most of the preparations on the market rely not on these agents, but on linoleic acid – one of the ingredients in corn oil – and other unsaturated fatty acids for their purported effect. The following are typical of proprietaries offered for the reduction of blood cholesterol: Saff (Abbott) – linoleic acid; Arcofac (Armour) – linoleic acid and pyridoxine; Linodoxine (Pfizer)– linoleic acid, pyridoxine, and tocopherols; Lenic (Crookes-Barnes) – mainly unsaturated fatty acids; Atheroxin (Gray) – corn oil and pyridoxine. Reliable evidence is lacking that the unsaturated fatty acids or corn oil in the amounts present in such preparations, or any of the other ingredients, alone or in combination, can achieve and maintain a reduced blood cholesterol level.

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